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Novel Ring Transformation of 3-Benzoylisoxazolidines into 2-Hydroxydihydrofurans. N-O Cleavage vs. 1,3-Dipolar Cycloreversion

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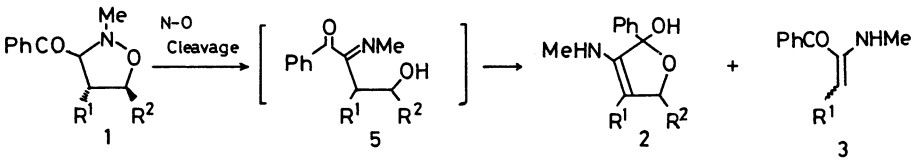
Thermal ring transformation of 3-benzoylisoxazolidines gives 2-hydroxydihydrofurans together with α-benzoylenamines, the product ratio of both compounds depending on the 4- and 5-substituents of the isoxazolidine ring. The ring transformation is in contrast to the case of analogous 3-phenylisoxazolidines, resulting in 1,3-dipolar cycloreversion.

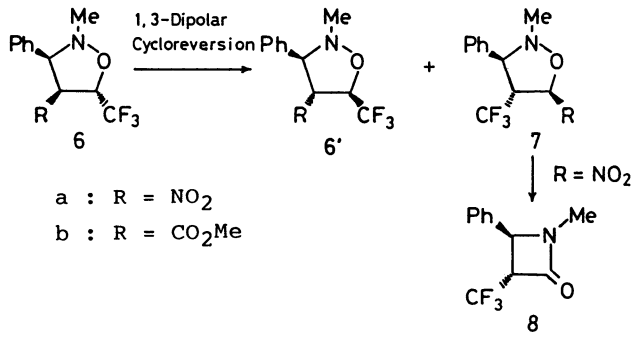
Recently considerable attention has been focused on the ring transformation of isoxazolidines for the synthesis of a variety of alkaloids, β-lactams, and other nitrogen-containing natural products.[1] The thermal ring transformation via N-O cleavage is, however, fairly limited to the isoxazolidines with 5-exo-methylene-, 5-nitro-, and 5-spiro-cyclopropyl substituents, being reorganized into pyrrolidinones,[2] β-lactams,[3] and tetrahydropyridones,[4] respectively. In connection with our research program to develop new synthetic method of fluorinated heterocycles,[5] we now report a novel ring transformation of 3-benzoylisoxazolidines, in which 3-benzoyl group participates to reorganization into 2-hydroxydihydrofurans. In contrast, 3-phenylisoxazolidines resulted in 1,3-dipolar cycloreversion,[6] giving their stereo- and regioisomeric isoxazolidines.

Refluxing of a solution of 3,4-trans-4,5-trans-3-benzoyl-2-methyl-4-nitro-5-trifluoromethylisoxazolidine (1a)[7] in dioxane for 45 h afforded 32% of 2-hydroxydihydrofuran 2a[8] consisting of two diasteroisomers (1/1 ratio) and 8% of α-benzoylenamine 3a together with 15% of β-trifluoroacetylenamine 4a.

Silica gel accelerated the reaction, giving 44% of 2a (1/1 diastereoisomer ratio) and 8 and 14% of 3a and 4a, respectively (reaction conditions; 50 °C, 37 h, in chloroform). Exclusive formation of the hydroxyfuran 2b (94% yield, 78/22 diastereoisomer ratio) was recognized from the 4-carboxylate analogue 1b under the similar conditions. Moreover, the product ratio of the hydroxyfuran 2 and the enamine 3 was found to be definitely dependent upon the 5-substituent of the isoxazolidine ring, as shown in Table 1. Thus the electron-withdrawing groups such as trifluoromethyl and ester groups depress the formation of the enamines 3. Reversely, phenyl group accelerates the enamine formation, and an effect of methyl group is just intermediate between the electron-withdrawing groups and the phenyl group.



	R^1	R^2
a	NO_2	CF_3
b	CO_2Me	CF_3
c	CO_2Me	CO_2Me
d	CO_2Me	Me
e	CO_2Me	Ph



a : R = NO_2
b : R = CO_2Me

The formation of the hydroxyfuran 2 can be explained by the intramolecular cyclization of the alcohol 5 which is derived via the N-O cleavage of the isoxazolidine 1 and a retro-aldol type reaction of the alcohol 5 would be one of the plausible reaction paths to the enamine 3.

On the other hand, heating of 3,4-cis-4,5-trans-3-phenylisoxazolidine-4-carboxylate (6b) resulted in 1,3-dipolar cycloreversion to give its stereoisomer

6'b and the regioisomer 7b.[9] Successive transformation of the regioisomer into the trans-β-lactam 8 was observed on heating (200 °C, 5 min) of 4-nitro analogue 6a, although the yield is as low as 19%.[10] The yield of 8, however, increased to 33%, 33% of 6'a being recovered, when the reaction of a 1/1 mixture of 6a and 6'a was carried out at 170 °C for 4 h in toluene in the presence of an equimolar amount of pyridine.

It should be noted that, the thermal ring transformation of isoxazolidines proceeds via either the N-O cleavage or 1,3-dipolar cycloreversion, depending on the 3-substituent of the isoxazolidine ring.

Table 1. Ring Transformation of 3-Benzoylisoxazolidines 1

	1[a]		Conditions[b]		Yield/%	
	R^1	R^2	Temp/°C	Time/h	2(ratio of diastereoisomers)	3(ratio of geometric isomers)
a	NO_2	CF_3	50	37	44(50/50)	8(one isomer)[c]
b	CO_2Me	CF_3	50	27	94(78/22)	---
c	CO_2Me	CO_2Me	ref.	24	65(one isomer)	---
d	CO_2Me	Me[d]	50	16	43(50/50)	46(80/20)
e	CO_2Me	Ph[d]	50	7	---	94(54/46)

a) 3,4-trans-4,5-trans-Isoxazolidine was used unless otherwise noted.
b) All reactions were carried out in chloroform in the presence of silica gel.
c) By-product 4a was isolated in 14% yield.
d) 3,4-cis-4,5-trans-Isoxazolidine was used.

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7) The isoxazolidines 1 and 6 were prepared by the cycloadditions of C-benzoyl- and C-phenyl-N-methylnitrones with the corresponding trans-olefins.

8) The hydroxyfuran 2a (1/1 mixture of diastereoisomers): mp 165-168 °C (dec.); ^{1}H NMR ($CDCl_3$-DMSO-d_6, TMS) δ=8.70 (br.s, 1H), 7.64-7.33 (m, 5H), 5.56 and 5.53 (q, 1H, J=5.4 and 5.4 Hz), 2.78 and 2.77 (d, 3H, J=5.7 and 5.8 Hz); IR (KBr) 3380 (OH), 3300 (NH), 1645 (C=C), 1170, 1130 cm^{-1} (CF_3); ^{13}C NMR ($CDCl_3$-DMSO-d_6, TMS) δ=159.2 and 158.0, 138.6 and 137.7, 129.7 and 129.6, 128.6, 128.5, 126.1 and 126.0, 127.6 and 123.4 (q, J=283.7 and 281.7 Hz), 112.6 and 111.5, 106.2 and 105.9, 76.4 and 76.1 (q, J=34.2 and 34.2 Hz), 30.4 and 30.1; Anal. Found: C, 47.42; H, 3.72; N, 9.25%. Calcd for $C_{12}H_{11}N_2O_4F_3$: C, 47.38; H, 3.64; N, 9.21%. All new other compounds gave satisfactory microanalytical data (within ±0.4% for C, H, N) and spectral data (IR, ^{1}H- and ^{13}C NMR). However, the isoxazolidine 7a could not be isolated and its structure was expected by the ^{1}H NMR analysis and its conversion into 8.

9) A solution of 6b, 6'b, and 7b (54/31/15) in the presence of toluene as an internal standard in deuteriochloroform was heated at 140 °C for 17 h in a sealed NMR tube and the ^{1}H NMR analysis of the resulting mixture showed 81% total yield of a mixture of 6b, 6'b, and 7b (6/60/34), accompanied by 14% of methyl trifluorobutenoate caused from 1,3-dipolar cycloreversion.

10) For the similar transformation of 5-nitroisoxazolidines into the corrresponding β-lactams, see Ref. 3.

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